39. The method of Claim 32 wherein the polypeptide, when expressed with a peptide comprising the amino acid sequence of SEQ ID NO: 3 and an IgG1 constant region, binds and inhibits hTNFα.

40. The method of Claim 34 wherein the polypeptide, when expressed with a peptide encoded by a nucleic acid molecule having the nucleotide sequence of SEQ ID NO: 4 and an IgG1 constant region, binds and inhibits hTNFα.

41. The method of Claim 36 wherein the polypeptide, when expressed with a peptide encoded by a nucleic acid molecule having the nucleotide sequence of SEQ ID NO: 2 and an IgG1 constant region, binds and inhibits hTNFα.

REMARKS

Specification Amendments

The Specification is amended to add low, medium and high stringency conditions. Support for this amendment is found, for example, in the Specification (at page 31, lines 5-10), which states "See, e.g., Ausubel *et al.*, eds. *Current Protocols in Molecular Biology*, Wiley Interscience, N.Y. (1987, 1992, 1993), and Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press (1989), the entire contents of which are incorporated herein by reference" and in Ausubel *et al.*, *supra*, at 2.10.2-2.10.3. The relevant portions of Ausubel *et al.* and Sambrook *et al.* are attached hereto as Exhibits A and B, respectively.

Claim Amendments

Claims 1, 2, 3, 5, 7, 8 and 17 are amended and Claims 18-41 are added.

Claims 1, 2, 7 and 8 are amended to recite that the hybridization is under conditions of high stringency to the complementary sequence of either SEQ ID NO: 2 or SEQ ID NO: 4 (depending on the claim or claim part). Support for these amendments is found throughout the Specification, for example on page 31, lines 5-10, page 32, lines 19-24 and page 34, lines 21-25, and in Ausubel *et al., supra,* (Exhibit A at 2.10.2-3 and 2.10.10-11) and Sambrook *et al., supra*, (Exhibit B at 11.45) incorporated by reference into the specification in their entirety at page 31, lines 5-10.

Claims 1-3, Claim 7, part (c) and Claim 8, part (c) are amended to clarify that the recited nucleic acid molecules, when expressed with a molecule having the sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and a gene encoding an IgG1 immunoglobulin constant region, encode a

polypeptide which binds hTNFα. Support for these amendments is found throughout the Specification, for example on page 35, line 11 to page 36, line 20.

Claim 5 is amended to clarify that the claimed nucleic acid molecule, when expressed with a molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 5 and a gene encoding an IgG1 immunoglobulin constant region, encodes a polypeptide which binds hTNFα. Claim 17 is amended to clarify that the recited polypeptide, when expressed with a peptide comprising the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 5 and an IgG1 constant region, binds to hTNFα. Support for these amendments is found throughout the Specification, for example on page 35, line 11 to page 36, line 20.

Claims 5 and 17 are also amended to delete reference to derivatives. Support for these amendment is found throughout the Specification, for example on page 19, lines 17-26.

Claims 18-22 are added. These claims are similar in scope to Claims 1, 2, 3, 7 (c), and 8 (c) and recite specific hybridization wash conditions. Support for these new claims is found throughout the Specification, for example on page 31, lines 5-10, page 32, lines 19-24 and page 34, lines 21-25, and in Ausubel *et al., supra* (See Exhibit A at 2.10.2-2.10.3), incorporated by reference into the Specification in its entirety at page 31, lines 5-10.

Claims 23-29 and 38-41 are added. These claims are similar in scope to Claims 1, 2, 3, 5, 7, 8, 17, 30, 32, 34 and 36 and contain the added limitation that the recited polypeptides inhibit hTNFα. Support for these new claims is found throughout the Specification, for example, on page 10, lines 4-15 and page 97, lines 3-23.

Claims 30-37 are added. Claims 30 and 32 claim methods of manufacturing a polypeptide comprising the amino acid sequence of SEQ ID NO: 3 (or SEQ ID NO: 5) or a fragment thereof wherein said polypeptide, when expressed with a peptide comprising the amino acid sequence of SEQ ID NO: 5 (or 3) and an IgG1 constant region, binds to hTNFα. These methods comprise expressing a nucleic acid molecule which encodes said polypeptide, said nucleic acid molecule operably linked to a promoter sequence, with a nucleic acid molecule encoding a peptide comprising the amino acid sequence of SEQ ID NO: 5 (or 3). Claims 34 and 36 claim methods of manufacturing a polypeptide encoded by a nucleic acid molecule having the nucleotide sequence of SEQ ID NO: 2 (or 4) or a fragment thereof wherein said polypeptide, when expressed with a peptide encoded by a nucleic acid molecule having the nucleotide sequence of SEQ ID NO: 4 (or 2) and an IgG1 constant region, binds to hTNFα. These methods comprise expressing a nucleic acid molecule having the nucleotide sequence of SEQ ID NO: 2 (or 4) or a fragment thereof, said nucleic acid molecule operably linked to a promoter sequence, with a nucleic acid molecule having the nucleotide sequence of SEQ ID NO: 4 (or 2). Support for these new claims is found throughout the Specification, for example, on page 35, line 11 to page 36, line 20, and in pending Claim 17.

Claims 31, 33, 35 and 37 are dependent on these method claims, and add the limitation that the nucleic acid molecule encoding the polypeptide is expressed with a gene encoding an IgG1 immunoglobulin constant region. Support for these new claims is found throughout the Specification, for example, on page 35, line 11 to page 36, line 20.

No new matter has been added by these amendment or new claims.

Rejection of Claims 1-3, 5, 7-11, 13 and 15-17 Under 35 U.S.C. §112, Second Paragraph

Claims 1-3, 5, 7-11, 13 and 15-17 are rejected under 35 U.S.C. §112, second paragraph on the grounds of being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

According to the Examiner, the recitations "selectively hybridizes" in Claims 1 and 2 and "specifically hybridize" in Claims 7 and 8 are vague and indefinite, the type of DNA hybridization that qualifies as selective or specific is unclear, and, absent the recitation of specific stringency conditions, the metes and bounds of the recitation "hybridizes" in Claims 1-2 and 7-8 and the recitation "hybridizes under conditions of moderate stringency" in Claim 3 are unclear.

Claims 1, 2, 7 and 8 are amended to recite that the hybridization occurs under conditions of high stringency. Claim 3 recites that the hybridization occurs under conditions of medium stringency. Claims 9-11, 15 and 16 are dependent upon Claims 1-3, 7 and 8 and contain the same limitations. Such hybridization conditions are well known to those of skill in the art. For example, stringent conditions are described in Sambrook, J. *et al.*, *supra,* at page 11.45 -11.61 ("Conditions for Hybridization of Oligonucleotide Probes") and Ausubel, F.N. *et al., Current Protocols in Molecular Biology*, at Chapter 2 ("Preparation and Analysis of DNA"), Chapter 14 ("In situ Hybridization and Immunochemistry") and Chapter 15 ("The Polymerase Chain Reaction"), Greene Publishing Assoc. and Wiley-Interscience (1989). Relevant portions of Chapter 2 of Ausubel *et al.* are included herein as Exhibit A. Relevant portions of Sambrook are included herein as Exhibit B. Hybridization conditions listed in these references include ionic strength and temperature of the post-hybridization wash. See, for example, Exhibit A at 2.10.2-3 and 2.10.10-11 and Exhibit B at 11.45. One skilled in the art would be able to optimize hybridization conditions by varying the specifically exemplified conditions discussed in the references and Specification. Such optimization is routine in the art.

The Examiner also states that "derivative" in Claims 5 and 17 is vague and indefinite on the grounds that the nature of the molecule or modification that qualifies as "derivative" is unclear. Claims 5 and 17 have been amended to delete the term "derivative" and Claim 13 is dependent upon Claim 5 and contains the same limitations. Consequently, this rejection is moot.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 2-3, 5, 10-11, 13 and 17 Under 35 U.S.C. §112, First Paragraph

Claims 2-3, 5, 10-11, 13 and 17 are rejected under 35 U.S.C. §112, first paragraph on the grounds that the "specification does not reasonably provide enablement commensurate with the scope of the claims." The Examiner believes that the specification does not enable any person skilled in the art to make or use the invention commensurate in scope with the claims because:

> Claims 2-3, 5, 10-11, 13 and 17 are broadly drawn to single polypeptides encoded by either SEQ ID NO: 2 or SEQ ID NO: 4, each polypeptide independently binding to TNFα. However, SEQ ID NO: 2 and SEQ ID NO: 4 encode, separately, the variable region of the heavy and light chains of an antibody with TNF specificity. It is well known in the art of immunology that both the heavy and light chains of an antibody together contribute to the antigen binding specificity of the intact antibody. Polypeptides comprising just the light chain variable region or just the heavy chain variable region rarely bind to antigen. Thus, one of skill in the art could not make and use the broadly claimed antibody with a reasonable expectation of success.

Claims 2 and 3 are amended to clarify that the encoded polypeptides bind to hTNFα when the molecules encoding them are expressed with a molecule having the sequence of SEQ ID NO: 2 or SEQ ID NO: 4 (depending on the claimed nucleic acid molecule) and a gene encoding an IgG1 immunoglobulin constant region. Claims 5 and 17 have been amended to clarify that the recited polypeptides bind to hTNFα when the molecules encoding them are expressed with a molecule encoding a peptide comprising the sequence of SEQ ID NO: 3 or SEQ ID NO: 5 and a gene encoding an IgG1 immunoglobulin constant region. Claims 10-11 and 13 are dependent upon Claims 2, 3 and 5, respectively, and contain the same limitations. Particularly as amended, these claims are enabled by the Specification.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 7 and 8 Under 35 U.S.C. §102(b)

Claims 1, 7 and 8 are rejected under 35 U.S.C. §102(b) as being anticipated either by page 167 of the 1994-1995 Promega Catalog or page 962 of Lehninger's Biochemistry Textbook (1975). According to the Examiner, page 167 of the Promega Catalog "discloses nucleic acid molecules (bulk dNTPs) which would hybridize to SEQ ID NO: 2 or SEQ ID NO: 4 and are the same as that claimed in claims 1, 7 (c) and 8 (c)" and Figure 34-1 of Lehninger's Biochemistry Textbook "also discloses nucleic acid molecules that would hybridize to SEQ ID NO: 2 or SEQ ID NO: 4 and are the same as that claimed in claims 1, 7 (c) and 8 (c)."

The 1994-1995 Promega catalog reference was published significantly later than the 1991 priority date of the subject application. Therefore, it does not qualify as a 102(b) anticipating reference. Furthermore, although the reference discloses "bulk dNTPs", it provides no sequences

or other structural or functional characteristics. The Lehninger reference at page 962, Figure 34-1, provides a "codon dictionary" which lists the codons that code for each amino acid.

Claim 7 (a) and (b) and Claim 8 (a) and (b) recite specific nucleic acid sequences and their complements. Neither these sequences nor their complements are disclosed in the cited references. Therefore, the references do not anticipate Claim 7 (a) or (b) or Claim 8 (a) or (b).

Claim 1, Claim 7 (c) and Claim 8 (c) are amended to recite nucleic acid sequences that hybridize, under conditions of high stringency, to the complementary sequence of SEQ ID NO: 2 (Claims 1 (a) and 7) or SEQ ID NO: 4 (Claims 1 (b) and 8), and which, when expressed with a molecule having the sequence of SEQ ID NO: 4 or SEQ ID NO: 2 and a gene encoding an IgG1 immunoglobulin constant region, encode a polypeptide which binds hTNFα. In contrast, the nucleic acid molecules disclosed in the references cited by the Examiner do not encode polypeptides which bind hTNFα under the claimed conditions. Therefore, the references do not anticipate Claim 1, Claim 7 (c) or Claim 8 (c).

Claims 7 (d) and 8 (d) recite RNA sequences transcribed from the sequences of parts (a), (b) or (c). For the same reasons that parts (a), (b) and (c) of Claim 7 and 8 are not anticipated, the RNA sequences transcribed from them are not anticipated.

Therefore, regardless of whether the cited molecules encode products which would hybridize to SEQ ID NO: 2 or SEQ ID NO: 4, the references do not anticipate the claimed molecules because they do not disclose every element of the claimed invention.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 9, 15 and 16 Under 35 U.S.C. §102(b)

Claims 9, 15 and 16 are rejected under 35 U.S.C. §102(b) as being anticipated by pages 152-153 of the 1993-1994 New England Biolabs Catalog. According to the Examiner, pages 152-153 disclose an expression vector comprising the single base pair sequences or triplet codons that qualify as "the nucleic acid molecule of Claims 1, 7 and 8," and, thus, are the same as that claimed.

The 1993-1994 New England Biolabs Catalog was published after the 1991 priority date of the subject application. Therefore, it does not qualify as a 102(b) anticipating reference. Furthermore, it does not disclose the claimed invention.

Claims 9, 15 and 16 claim an expression vector comprising the nucleic acid molecule according to Claims 1, 7 and 8, respectively. Claim 7 (a) and (b) and Claim 8 (a) and (b) recite specific nucleic acid sequences and their complements. Neither these sequences nor their complements are disclosed in the cited reference. Therefore, the reference does not anticipate Claims 15 and 16 to the degree that these claims pertain to Claim 7 (a) or (b) or Claim 8 (a) or (b).

Furthermore, as stated above, Claims 1, 7 (c) and 8 (c) are amended to recite nucleic acid sequences that hybridize, under conditions of high stringency, to the complementary sequence of SEQ ID NO: 2 (Claims 1 (a) and 7) or SEQ ID NO: 4 (Claims 1 (b) and 8), and which, when expressed with a vector having the sequence of SEQ ID NO: 4 or SEQ ID NO: 2 and a gene encoding an IgG1 immunoglobulin constant region, encode a polypeptide which binds hTNFα. In contrast, the nucleic acid vectors disclosed in the reference cited by the Examiner do not comprise sequences which encode polypeptides which bind hTNFα under the claimed conditions. Therefore, the reference does not anticipate Claims 15 and 16 to the degree that these claims pertain to Claim 1, Claim 7 (c) or Claim 8 (c).

Claims 7 (d) and 8 (d) recite RNA sequences transcribed from the sequences of parts (a), (b) or (c). For the same reasons that the reference does not anticipate Claims 15 and 16 to the degree that these claims pertain to parts (a), (b) and (c) of Claims 7 and 8, it does not anticipate Claims 15 and 16 to the degree that they pertain to RNA sequences transcribed from parts (a), (b) and (c).

Therefore, regardless of whether the cited vectors encode products which would hybridize to SEQ ID NO: 2 or SEQ ID NO: 4, the reference does not anticipate the claimed vectors because it does not disclose every element of the claimed invention.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 7, 8, 9, 15 and 16 Under 35 U.S.C. §102(b)

Claims 1, 7, 8, 9, 15 and 16 are rejected under 35 U.S.C. §102(b) as being anticipated by either of Accession number M32046 (15 June 1990) or N90300 (1 Nov. 1989). According to the Examiner, both Accession Nos. disclose a nucleic acid molecule that would hybridize to either SEQ ID NO: 2 or SEQ ID NO: 4 and expression vectors comprising said molecules, that are the same as that claimed. The references state that they disclose sequences for an insert coding for light chain variable region, with a query match of 90.7 % compared with SEQ ID NO: 2 (N90300) and a mouse Ig active H chain mRNA V-region with a query match of 72.0 % compared with SEQ ID NO: 4 (M32046).

Claim 7 (a) and (b) and Claim 8 (a) and (b) recite specific nucleic acid sequences and their complements. Neither these sequences nor their complements are disclosed in the cited references. Therefore, the references do not anticipate Claim 7 (a) or (b) or Claim 8 (a) or (b).

The only parts of Claim 7 and 8 that recite hybridizing molecules are 7 (c) and 8 (c). As stated above, Claims 1, 7 (c) and 8 (c) are amended to recite nucleic acid sequences that hybridize, under conditions of high stringency, to the complementary sequence of SEQ ID NO: 2 (Claims 1(a) and 7) or SEQ ID NO: 4 (Claims 1(b) and 8), and which, when expressed with a nucleic acid molecule having the sequence of SEQ ID NO: 4 or SEQ ID NO: 2 and a gene

encoding an IgG1 immunoglobulin constant region, encode a polypeptide which binds hTNFα. Claims 9, 15 and 16 claim an expression vector comprising the nucleic acid molecule according to Claims 1, 7 and 8, respectively. In contrast, the nucleic acid molecules and vectors disclosed in the reference cited by the Examiner do not comprise sequences which encode polypeptides which bind hTNFα under the recited conditions.

Claims 7 (d) and 8 (d) recite RNA sequences transcribed from the sequences of parts (a), (b) or (c). For the same reasons that parts (a), (b) and (c) of Claim 7 and 8 are not anticipated, the RNA sequences transcribed from them are not anticipated.

Therefore, regardless of whether the cited molecules and vectors comprise sequences which encode products which would hybridize to SEQ ID NO: 2 or SEQ ID NO: 4, the references do not anticipate the claimed molecules and vectors because they do not disclose every element of the claimed invention.

Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

It is respectfully submitted that the claims are now in condition for allowance. If the Examiner feels that a telephone conversation with Applicants' Attorney would be helpful in expediting the prosecution of this case, the Examiner is encouraged to call Applicants' Attorney at (781) 861-6240.

Respectfully submitted,

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